REMARKS

Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 50-1213.

Claims 1-18, 20, 21 and 31-41 are pending and deemed allowable. Claims 1 and 18 are amended herein to correct minor typographical errors. Claim 31 is amended herein to more particularly point out and distinctly claim the subject matter by including the recitation "the concentration of" preceding the recitation –circulating targeted photosensitizer compound–, basis for which is found throughout the specification (for example, see page 8, lines 1-6). No new matter is added. Entry of the amendment is respectfully requested.

COMMENTS ON EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE

In the statement of reasons for allowance, the Examiner states that none of the prior art of record discloses or suggests a method for administering a photodynamic therapy (PDT) to destroy or impair target cells expressing a VEGF receptor that includes in part the combination of the steps of (a) administering to the subject a therapeutically effective amount of a targeted photosensitizer compound having a characteristic light absorption waveband, where the targeted photosensitizer compound selectively binds with the target cells, but does not bind with non-target cells, and the photosensitizer compound is targeted to a VEGF receptor; and (b) transcutaneously irradiating at least a portion of the mammalian subject in which the target cells to which the targeted photosensitizer compound has bound are disposed, with light having a waveband corresponding at least in part to the characteristic light absorption waveband of the targeted photosensitizer compound, where the intensity of the light used for the step of irradiating and the duration of irradiation are selected such that the target cells are destroyed and the non-target tissue through which the light passes remains undamaged. In addition, none of the art of record, singly or in any combination thereof discloses, teaches or suggests for the step of irradiating that the intensity and the duration of irradiation "are selected such that the target cells are

destroyed and the non-target tissue through which the light passes remains undamaged."

The Examiner states that Watson (U.S. Patent No. 5,053,006) and Peyman *et al.* (U.S. Patent No. 6,162,242) are considered pertinent. Watson discloses a method for the permanent occlusion of arteries via the irradiation of target cells injected with rose bengal photosensitizer with light of a wavelength sufficient to excite the rose bengal molecules. The Examiner states that Watson lacks the disclosure of transcutaneous irradiation. In addition, Watson does not disclose other elements of the claims including use of a targeted photosensitizer compound or targeting of a VEGF receptor. Peyman discloses a selective photodynamic treatment of the eye using a photosensitizing agent and pressure-induced collapse of the intraocular vessels. Peyman does not disclose transcutaneous irradiation, a targeted photosensitizer compound or targeting a VEGF receptor.

Neither reference teaches or suggests for the step of irradiating that the intensity and the duration of irradiation "are selected such that the target cells are destroyed and the non-target tissue through which the light passes remains undamaged." Thus, neither of these references, nor any art of record, singly or in any combination thereof, teaches or suggests the claimed methods.

REJECTIONS FROM U.S. APPLICATION SERIAL NO. 09/386,692

In compliance with our duty of disclosure, the Examiner's attention is directed to co-pending U.S. Application Serial No. 09/386,692, filed August 31, 1999, which is being examined by Art Unit 1614. To insure a complete record in this application, the responses of record in U.S. Application Serial No. 09/386,692 are herein incorporated by reference. Applicant respectfully submits that all of the art cited in the rejections in co-pending U.S. Application Serial No. 09/386,692 was made of record in the instant case. The outstanding rejections in that application that rely on art not relied on by the Office in this case are addressed below.

CHAN *et al.* - REJECTION UNDER 35 U.S.C. §102(b)

Claim 4 in co-pending U.S. Application Serial No. 09/386,692 is rejected under 35 U.S.C. § 102(b) as anticipated by Chan *et al.*, which allegedly discloses using green porphyrins as antigen-specific immunomodulators in the active phase of an immune response to a particular antigen and activating the green porphyrins using ambient light at levels that are greater than 50 Joules.

To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981).

Moreover, it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Disclosure of Chan *et al.*

Chan *et al.* discloses using green porphyrins with ambient light to influence an immune response against a specific antigen, and for treating conditions associated with an unwanted immune response, including allograft transplants, rheumatoid arthritis, multiple sclerosis, psoriasis, lupus and allergic reactions (col.

3, lines 17-52). Chan *et al.* discloses that its photosensitizers can modulate an immune response when activated under conditions of ambient light (col. 4, lines 38-40). Chan *et al.* discloses that a specific protocol is not necessary to supply ambient light (col. 8, lines 53-54).

Differences between the claimed subject matter and the disclosure of Chan *et al.*

Chan *et al.* does not disclose destroying or impairing target cells expressing a VEGF receptor. Chan *et al.* does not disclose selecting an intensity and duration of light for irradiating to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed, and the healthy non-target tissue through which the light passes remains undamaged. Instead, Chan *et al.* discloses that no specific protocol to supply ambient light is necessary. There is no mention of any significance of the parameters of light intensity and/or duration of irradiation. Chan *et al.* does not disclose selecting a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of PDT to achieve target cell destruction without damage to non-target tissue. Hence, Chan *et al.* does not disclose selecting a combination of a light intensity and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed, and the healthy non-target tissue remains undamaged. Further, Chan *et al.* does not disclose a method of PDT that includes administering a first and second conjugate as instantly claimed. Chan *et al.* does not disclose occluding a blood vessel using a photosensitizer compound.

Therefore, because Chan *et al.* does not disclose every element of the claimed subject matter of allowed independent claims 1, 16, 18 or 31, Chan *et al.* does not anticipate any of the allowed claims.

LEVY *et al.* - REJECTION UNDER 35 U.S.C. §102(b)

Claims 1 and 4 in co-pending U.S. Application Serial No. 09/386,692 are rejected under 35 U.S.C. § 102(b) as anticipated by Levy *et al.* (U.S. 6,100,290) because Levy *et al.* allegedly discloses photodynamic therapy for multiple

sclerosis and rheumatoid arthritis and reducing the population of leukocytes using a number of photoactive agents that when irradiated results in cytotoxicity to the surrounding tissue. To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

Disclosure of Levy *et al.*

Levy *et al.* discloses a method of treating a subject with an immune dysfunction, such as multiple sclerosis and rheumatoid arthritis, by selectively lowering the population of activated leukocytes in the subject. Levy *et al.* discloses using wavelengths in the 670-780 nm range with typical intensities between 1-500 J/cm^2 and a duration of between 2-180 minutes (col. 13, lines 17-24). Levy *et al.* discloses that selection of intensity depends on the width of the wavelength band (col. 13, lines 17-18). The reference discloses that duration of irradiation depends on the nature and concentration of the photoactive agent in the bloodstream and the susceptibility to the treatment (col. 13, lines 20-24). Levy *et al.* discloses that when green porphyrins are irradiated *in situ* using light in the visible absorption range, photoactivation results in cytotoxicity to the surrounding tissue (col. 6, lines 8-13). Levy *et al.* discloses that it is unnecessary to allow sufficient time for unbound sensitizer to clear from non-target tissue before photoactivation (col. 14, lines 56-63).

Differences between the claimed subject matter and the disclosure of Levy *et al.*

Levy *et al.* does not disclose destroying or impairing target cells expressing a VEGF receptor. Levy *et al.* does not disclose selecting an intensity of the light used for the step of irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed, and the healthy non-target tissue through which the light passes remains undamaged. Levy *et al.* discloses that selection of intensity depends on the width of the wavelength band and that duration of irradiation depends on the nature and concentration of the photoactive agent in the bloodstream and the susceptibility to the treatment. There is no mention of any significance of the parameters of light intensity and/or duration of irradiation,

nor is there any discussion on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target tissue destruction without damage to non-target tissue. In fact, Levy *et al.* discloses that when green porphyrins are irradiated *in situ* using light in the visible absorption range, photoactivation results in cytotoxicity to the surrounding tissue. Thus, Levy *et al.* does not disclose selecting a combination of intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed while the non-target tissue through which the light passes remains undamaged. Further, Levy *et al.* does not disclose a method of photodynamic therapy that includes administering a first and second conjugate as instantly claimed, nor does the reference disclose occluding a blood vessel using a photosensitizer compound.

Therefore, because Levy *et al.* does not disclose every element of the claimed subject matter of allowed independent claims 1, 16, 18 or 31, Levy *et al.* does not anticipate any of the allowed claims.

TRAUNER *et al.* - REJECTION UNDER 35 U.S.C. §102(b)

Claims 1 and 4 in co-pending U.S. Application Serial No. 09/386,692 are rejected under 35 U.S.C. § 102(b) as anticipated by Trauner *et al.* (U.S. 5,942,534) because Trauner *et al.* allegedly discloses a method of PDT to treat osteoarthritic disease using any one of a number of disclosed compounds for photodynamic therapy using light of the appropriate wavelength administered by a variety of methods known to one skilled in the art. To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

Disclosure of Trauner *et al.*

Trauner *et al.* discloses treating osteoarthritic disease using a photo-activatable compound and using an appropriate wavelength of light for activation. Trauner *et al.* discloses using a total light energy of 100 J/cm^2 or an energy range deemed appropriate for a given compound, and irradiation for 20 minutes with an average power setting of 3-5 watts, or that wattage and time that is effective for

a given compound (col. 8, lines 13-20). Trauner *et al.* discloses light dosage studies and toxicity studies to determine cellular viability (col. 11, line 60 through col. 12, line 15). The reference discloses administering light of the appropriate wavelength using laser, non-laser, or broad band light that is generated either extracorporeally or intra-articularly (col. 3, line 64 through col. 4, line 2). Trauner *et al.* discloses that a test compound that diminishes inflammation without concomitant deleterious effects on articular cartilage, meniscus and other periarticular tissues could be a useful compound for PDT (col. 8, lines 62-67).

Differences between the claimed subject matter and the disclosure of Trauner *et al.*

Trauner *et al.* does not disclose destroying target cells expressing a VEGF receptor. Trauner *et al.* does not disclose selecting an intensity and duration of light for irradiating to produce a total fluence of light sufficient to activate the photosensitizer compound such that the target cells are destroyed, and the healthy non-target tissue through which the light passes remains undamaged. Trauner *et al.* discloses light dosage studies and toxicity studies to determine cellular viability. There is no mention of any significance of the parameters of light intensity and/or duration of irradiation, nor is there any mention or discussion on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target tissue destruction without damage to non-target tissue. Trauner *et al.* does not disclose varying the parameters of light intensity and duration of irradiation to determine whether a test compound that causes deleterious effects on articular cartilage or other periarticular tissues could be a useful compound for PDT under a different selected combination of light intensity and duration of irradiation. Hence, Trauner *et al.* does not disclose selecting a combination of an intensity of light for irradiation and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed while the healthy non-target tissue through which the light passes remains undamaged. Further, Trauner *et al.* does not disclose a method of

photodynamic therapy that includes administering a first and second conjugate as instantly claimed, nor does the reference disclose occluding a blood vessel using a photosensitizer compound.

Therefore, because Trauner *et al.* does not disclose every element of the claimed subject matter of allowed independent claims 1, 16, 18 or 31, Trauner *et al.* does not anticipate any of the allowed claims.

LEONG *et al.* - REJECTION UNDER 35 U.S.C. §102(b)

Claims 1 and 4 in co-pending U.S. Application Serial No. 09/386,692 are rejected under 35 U.S.C. § 102(b) as anticipated by Leong *et al.* (U.S. 5,807,881) because Leong *et al.* allegedly discloses photodynamic methods for selectively depleting blood or bone marrow cells in immune dysfunctional disorders by irradiating using a fiber-optic device inserted into the bloodstream or by external light exposure, using typical intensities of light between 8-15 J/cm^2 for preferably about 15-20 minutes. To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

Disclosure of Leong *et al.*

Leong *et al.* discloses a method to selectively lower the population of activated leukocytes in subjects showing elevated levels of leukocyte activation markers. Leong *et al.* discloses using an appropriate wavelength with typical intensities between 1-500 J/cm^2 and a duration of between about 2-180 minutes (col. 12, lines 49-58). Leong *et al.* discloses that selection of intensity depends on the width of the wavelength band (col. 12, lines 51-52). The reference discloses that duration of irradiation depends on the nature and concentration of the photoactive agent in the bloodstream and the susceptibility to the treatment (col. 12, lines 55-58). Leong *et al.* discloses that when green porphyrins are irradiated *in situ* using light in the visible absorption range, photoactivation results in cytotoxicity to the surrounding tissue (col. 6, lines 1-3). Leong *et al.* discloses that it is unnecessary to allow sufficient time for unbound sensitizer to clear from non-target tissue before photoactivation (col. 14, lines 19-26).

Differences between the claimed subj ct matter and the disclosure of Leong *et al.*

Leong *et al.* does not disclose destroying or impairing target cells expressing a VEGF receptor. Leong *et al.* does not disclose selecting an intensity of the light used for the step of irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed, and the healthy non-target tissue through which the light passes remains undamaged. Leong *et al.* discloses that selection of intensity depends on the width of the wavelength band and that duration of irradiation depends on the nature and concentration of the photoactive agent in the bloodstream and the susceptibility to the treatment. There is no mention of any significance of the parameters of light intensity and/or duration of irradiation, nor is there any mention or discussion on the selection of a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target cell destruction without damage to non-target tissue. Further, Leong *et al.* discloses that when green porphyrins are irradiated *in situ*, photoactivation results in cytotoxicity to the surrounding tissue. Thus, Leong *et al.* does not disclose selecting a combination of intensity of light used for irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed while the healthy non-target tissue remains undamaged. Further, Leong *et al.* does not disclose a method of photodynamic therapy that includes administering a first and second conjugate as instantly claimed, nor does the reference disclose occluding a blood vessel using a photosensitizer compound.

Therefore, because Leong *et al.* does not disclose every element of the claimed subject matter of allowed independent claims 1, 16, 18 or 31, Leong *et al.* does not anticipate any of the allowed claims.

RICHTER - REJECTION UNDER 35 U.S.C. §102(b)

Claim 4 in co-pending U.S. Application Serial No. 09/386,692 is rejected under 35 U.S.C. § 102(b) as anticipated by Richter (U.S. 5,736,563) because

Richter allegedly discloses a method to destroy or impair target cells that have selectively accumulated a photosensitizing agent by using light of the appropriate wavelength. To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

Disclosure of Richter

Richter discloses a method to destroy or impair blood-borne target cells that have selectively accumulated a photosensitizing agent while leaving non-target cells relatively unimpaired by transcutaneously applying radiation of the appropriate wavelength (col. 2, lines 61-67). Richter discloses that the intensity of radiation within the bloodstream is between about 2 and 150 mW/cm^2 and that the duration of radiation exposure is between about 0.25 minute and 24 hours (col. 5, lines 12-16). Richter discloses that damage to skin is determined by the maximum plasma concentration of the photosensitizer, the length of time between injection of the photosensitizer and subsequent exposure to light, and the intensity of the light used (col. 12, lines 17-21).

Differences between the claimed subject matter and the disclosure of Richter

Richter does not disclose destroying or impairing target cells expressing a VEGF receptor. Richter does not disclose selecting an intensity of the light used for the step of irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed while the healthy non-target tissue through which the light passes remains undamaged. Richter discloses various ranges of intensity of radiation and ranges of duration of radiation. There is no mention of any significance of the combination of light intensity and duration of irradiation, nor is there any mention or discussion on the selection of a combination of these two parameters in further combination with the use of a targeted photosensitizer compound for use in methods of photodynamic therapy to achieve target cell destruction without damage to non-target tissue through which the light passes. Instead, the reference discloses that damage to non-target tissue is determined by the plasma concentration of the photosensitizer, the length of time between

injection of the photosensitizer and exposure to light, and the intensity of the light used. Richter does not disclose a method in which target tissue is destroyed while healthy non-target tissue through which the light passes remains undamaged, because Richter discloses that its method can produce severe skin necrosis (col. 10, lines 43-48). Further, Richter does not disclose a method of photodynamic therapy that includes administering a first and second conjugate as instantly claimed, nor does the reference disclose occluding a blood vessel using a photosensitizer compound. Richter discloses a method to destroy or impair blood-borne target cells and thus teaches away from occluding blood vessels.

Therefore, because Trauner *et al.* does not disclose every element of the claimed subject matter of allowed independent claims 1, 16, 18 or 31, Trauner *et al.* does not anticipate any of the allowed claims.

SELMAN IN VIEW OF LAWANDY - REJECTION UNDER 35 U.S.C. §103(a)

Claims in co-pending U.S. Application Serial No. 09/386,692 are rejected under 35 U.S.C. §103(a) as being unpatentable over Selman (U.S. 5,514,669) in view of Lawandy (U.S. 5,817,048), because Selman allegedly teaches a method of photodynamic therapy to treat sensitized prostatic tissue using light, and Lawandy teaches the use of ultrasonic energy in photodynamic therapies. To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ

871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp*. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

TEACHINGS OF THE CITED REFERENCES

Selman

Selman teaches a method for diagnosing or treating prostatic tissue, which includes sensitizing noncancerous prostatic tissue with an effective amount of a photosensitizer which accumulates in the tissue, and exposing the sensitized tissue to a source of light for a predetermined length of time and wavelength, whereby the photosensitizer in the light-exposed tissue absorbs the light or undergoes a photochemical reaction (see claim 1). Selman teaches that the particular wavelength and intensity of light energy delivered to the tissue is dependent upon the type of photosensitive composition being used (col. 3, lines 53-56). Selman teaches intensities of light illumination in the range of 15 to about 500 Joules (col. 4, lines 58-60). Selman teaches irradiating the photosensitive compositions for times of one hour or less to as long as three to four days (col. 3, lines 35-40). Selman teaches that components may be chemically attached to or physically combined with the photosensitive composition to enhance the selectivity of the photosensitizer for the target tissue (col. 3, line 65 through col. 4, line 5).

Lawandy

Lawandy teaches a method of using ultrasound as an alternative to laser-based PDT by administering a photosensitive therapeutic compound in a hydrogen-rich solvent in combination with an oxalate ester, and generating acoustic energy to form free radicals, which react with the oxalate ester to

generate a key intermediate. The intermediate then transfers chemical energy to the photosensitizer to activate it, thereby resulting in cellular destruction.

The combination of teachings of Selman with the teachings of Lawandy does not result in the instantly claimed methods

VEGF Receptors

Selman teaches including labeling compositions such as receptor ligands to enhance the photosensitive composition's selectivity for the prostate, but Selman does not teach or suggest destroying or impairing target cells that express a VEGF receptor. Lawandy does not cure this defect. Lawandy does not teach or suggest using a targeted photosensitizer, or targeting specific receptor ligands, or destroying or impairing target cells that express a VEGF receptor.

Combining the teachings of Selman and Lawandy does not teach or suggest every element of the subject matter claimed in the instant application. Neither Selman nor Lawandy, alone or in combination, teaches or suggests targeting specific receptor ligands, or destroying or impairing target cells that express a VEGF receptor. Thus, combining the teachings of Selman and Lawandy does not result in the subject matter of allowed claims 1-18, 20 and 21.

Selecting a Combination of Irradiation Intensity and Duration

Selman does not teach or suggest that, in a method of PDT using a targeted photosensitizer compound, the parameters of irradiation intensity and irradiation duration can be varied and selected to achieve destruction of a target cell without damage to a non-target tissue through which the light passes during irradiation. Selman provides little, if any, guidance on the combination of light/energy intensities and duration of irradiation to be used in therapeutic methods involving photosensitive compositions. Selman states only generally that

> [i]t is contemplated that various protocols of treatment using the method of the present invention may involve illuminating the photosensitive compositions for time periods ranging from a relatively short time of approximately one hour or less to a longer time of three to four days (col. 3, lines 34-39),

and that

> the tissue is irradiated with light of a predetermined wavelength at which the composition shows absorbance peaks optimum for fluorescence excitation or, using another wavelength, for tissue destruction. This absorption of light energy by the photosensitive composition causes a reaction which destroys the tissue in which the composition has accumulated and the light is delivered. It is to be understood that the particular wavelength delivered to the tissue is dependent, in part, upon the type of photosensitive composition being used. In certain embodiments, photosensitive compositions which have absorbance peaks at longer wavelengths and show greater absorbencies may be used. In various embodiments, the longer wavelength peaks are advantageous because the light of the longer wavelengths is capable of greater penetration of tissue, while the greater absorbencies are desirable because less light energy is required to cause a given degree of reaction. (col. 3, lines 45-64).

There is no teaching or suggestion in Selman that, in conducting PDT, there are combinations of the parameters of light intensity and duration of irradiation that can be selected, which, when used in conjunction with a targeted photosensitizer compound, provide a total fluence that achieves destruction of the target cells without damage to a non-target tissue. Instead, Selman only lists light sources that may be used, *e.g.*, laser, LED device, or lamp (col. 7, lines 12-18), and teaches a range of light intensities (col. 4, lines 58-60).

There is no mention of any significance of the parameters of light intensity and/or duration of irradiation. Selman does not teach or suggest selecting a combination of these parameters in further combination with the use of a targeted photosensitizer compound for use in methods of PDT to destroy target tissue without damaging non-target tissue. Selman teaches that damage to non-target tissue will occur using its PDT method taught, unless measures are taken to prevent rogue light from activating photosensitizer compounds taken up by non-target tissue. Selman teaches minimizing damage to non-target tissues by accurately positioning the light delivery means to limit penetration of light into non-target tissue so that only the target tissue is irradiated (col. 5, lines 45-48), or coating the end of the light delivery means to prevent light from penetrating beyond the target tissue area (col. 9, line 66 through col. 9, line 1).

Selman teaches in Example 1b that extensive mucosal and submucosal hemorrhage occurred in non-target tissue in two of the test animals, which Selman attributes to animal movement or inaccurate placement of the light guide during treatment (col. 11, lines 1-6). Selman does not teach or suggest that varying the intensity of the light used for activation, or varying the duration of irradiation, or combinations thereof, can be used to minimize non-target tissue damage. Selman teaches that merely controlling the direction of the illuminating light is sufficient to minimize collateral tissue damage. Selman does not vary the power density of the light used to activate the photosensitizer, and Selman does not teach any such variation, and provides no motivation to do so.

There is no mention of any other intensities/durations and combinations thereof and/or the effects of the specific intensity (or other intensities) and duration (or other durations) on target tissue and/or non-target tissue destruction. Thus, there is no suggestion, much less teaching, in Selman of the significance in photodynamic therapy using a targeted photo-reactive compound of the parameters of light intensity and the duration of irradiation. There is no teaching or suggestion that combinations of the parameters of light intensity and light duration can be determined that provide a total fluence that achieves destruction of a target tissue or target cell without damage to non-target tissue.

Lawandy does not cure these defects. Lawandy contains minimal teaching of the parameters of the intensity of light or acoustic energy used, and provides no teaching or suggestion on the duration of the irradiation for photodynamic therapy. Lawandy teaches generating acoustic energy for producing free radicals from a hydrogen-containing solvent (col. 1, lines 51-54). Nowhere in Lawandy is it suggested that when using light irradiation (or even ultrasonic irradiation) to produce a therapeutic outcome, the parameters of light/energy intensity and the duration of irradiation can be varied and selected in combination with the use of a targeted energy-reactive compound to provide a total fluence that achieves destruction of a target tissue or a target cell without damage to non-target tissue. In fact, collateral damage to non-target tissue is minimally discussed, if at all, in Lawandy.

In addition, Lawandy provides little to no guidance in determining the radiation parameters. The only detail provided in Lawandy as to light/energy dose is that ALA and PHOTOFRIN®, PDT drugs known in the art, have a peak absorption of 630 nm (col. 4, lines 4-8), and that an ultrasound transducer can be operated in the kilohertz to megahertz range (col. 2, lines 43-47). Lawandy does not teach or suggest the energy level to be used *in vivo*. The information in this reference fails to provide any guidance as to the intensity of light/energy that should be used.

Further, Lawandy does not teach or suggest the duration of irradiation that should be used to obtain the stated energy and effects in PDT. Lawandy teaches that H_2O_2 is produced at a rate of $8.4x10^{-5}$M/min in pure DMP solvent (col. 2, lines 52-56), but does not teach the minimum effective amount of H_2O_2 required for treatment, nor the time necessary to generate such an effective amount. Lawandy does not teach any combination of energy intensities or durations of irradiation, or the effects of any intensity and duration on target tissue and/or non-target tissue destruction.

Neither Selman nor Lawandy, alone or in combination, teaches or suggests selecting a combination of intensity and duration of light/energy used for irradiating to produce a total fluence of light/energy sufficient to activate the photosensitizer compound such that the target cells are destroyed and the healthy non-target tissue remains undamaged. Thus, combining the teachings of Selman and Lawandy does not result in the subject matter of allowed claims 1-18, 20, 21 and 31-41.

TRAUNER IN VIEW OF LAWANDY - REJECTION UNDER 35 U.S.C. §103(a)

Claims in co-pending U.S. Application Serial No. 09/386,692 are rejected under 35 U.S.C. §103(a) as being unpatentable over Trauner *et al.* (U.S. 5,942,534) in view of Lawandy (U.S. 5,817,048), because Trauner *et al.* allegedly teaches a method of PDT that includes all elements of the claimed subject matter except that Trauner *et al.* does not specifically teach treatment of tumors and a time limitation for light therapy after administration of the

photosensitizer, but Lawandy *et al.* allegedly cures these defects. To the extent this applies to any claims pending herein, this rejection is respectfully traversed.

TEACHINGS OF THE CITED REFERENCES

See related sections above.

ANALYSIS

The combination of teachings of Trauner with the teachings of Lawandy does not result in the instantly claimed methods

VEGF Receptors

Trauner does not teach or suggest targeting cells with specific receptors or ligands, and does not teach or suggest destroying or impairing target cells that express a VEGF receptor. Lawandy does not cure this defect. Lawandy does not teach or suggest using a targeted photosensitizer, or targeting specific receptor ligands, or destroying or impairing target cells that express a VEGF receptor.

Combining the teachings of Trauner and Lawandy does not teach or suggest every element of the subject matter claimed in the instant application. Neither Trauner nor Lawandy, alone or in combination, teaches or suggests destroying or impairing target cells that express a VEGF receptor. Thus, combining the teachings of Selman and Lawandy does not result in the subject matter of allowed claims 1-18, 20 and 21.

Selecting a Combination of Irradiation Intensity and Duration

As discussed above in the traverse of Trauner under § 102, Trauner does not teach or suggest selecting an intensity of the light used for the step of irradiating and a duration of irradiation to produce a total fluence of the light sufficient to activate the photosensitizer compound such that the target cells are destroyed, and the healthy non-target tissue through which the light passes remains undamaged. Lawandy does not cure this defect. As discussed above in the traverse of Selman/Lawandy, Lawandy does not teach any combination of energy intensities or durations of irradiation, or the effects of any intensity and duration on target tissue and/or non-target tissue destruction.

Combining the teachings of Trauner and Lawandy does not teach or suggest every element of the subject matter claimed in the instant application. Neither Trauner nor Lawandy, alone or in combination, teaches or suggests selecting a combination of intensity of light/energy used for irradiating and a duration of irradiation to produce a total fluence of light/energy sufficient to activate the photosensitizer compound such that the target cells are destroyed and the healthy non-target tissue remains undamaged through which the light/energy passes remains undamaged. Thus, combining the teachings of Trauner and Lawandy does not result in the subject matter of allowed claims 1-18, 20, 21 and 31-41.

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Applicant respectfully requests entry of the above amendments and remarks into the file history of the above-captioned application.

Respectfully submitted,
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By: _____
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